LUTONIX® 035 Drug Coated Balloon PTA Catheter

INSTRUCTIONS FOR USE

Caution: Federal Law (USA) restricts this device to sale by or on the order of a physician.

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1 DEVICE DESCRIPTION

1.1 PTA Catheter Description

The LUTONIX® 035 Drug Coated Balloon PTA Catheter (LUTONIX® Catheter) consists of an over the wire catheter with a drug coated balloon fixed at the distal tip. The balloon is coated with a specialized formulation that includes the anti-proliferative drug, paclitaxel. The LUTONIX® Catheter is 0.035" guidewire compatible, with a low profile, semi-compliant balloon formed to a low profile tapered tip to facilitate advancement of the catheter to and through the stenotic region of the vessel. Two radiopaque marker bands delineate the working length of the balloon and are located under the proximal and distal ends of the balloon to facilitate fluoroscopic visualization of the balloon during delivery and placement. The proximal portion of the catheter includes an inflation female luer lock hub and a guidewire female luer lock hub. Each product is packaged with a balloon protector that has been positioned over the balloon and a disposable wire lumen stylet, both of which are to be removed prior to use.

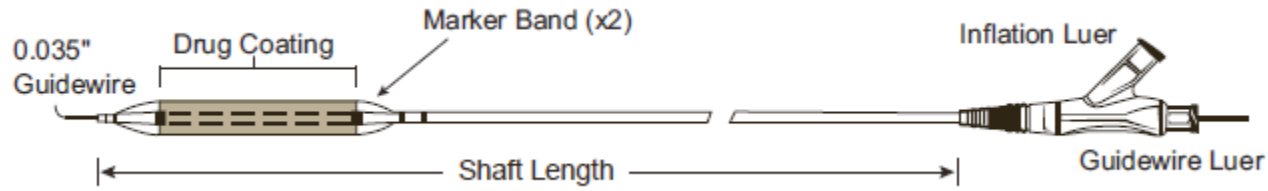


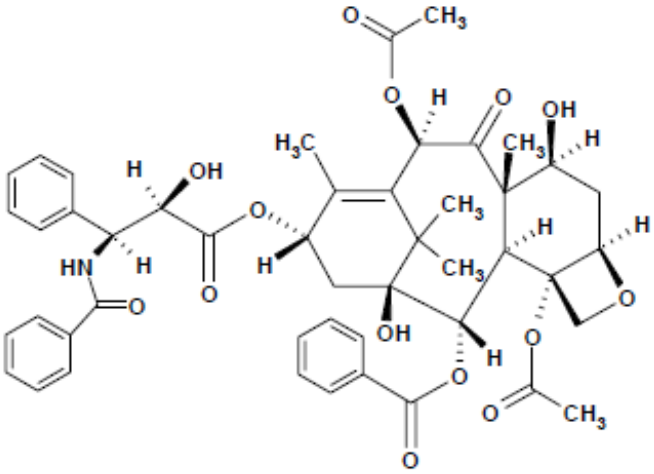
Figure 1. Lutonix® 035 Drug Coated Balloon PTA Catheter, Model 9004

Table 1. Lutonix® 035 Drug Coated Balloon PTA Catheter Product Description

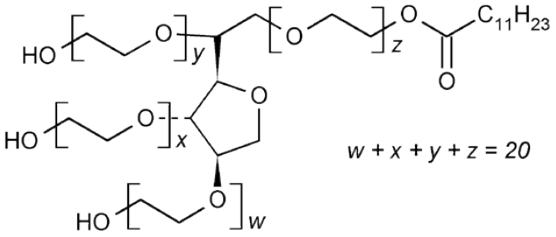
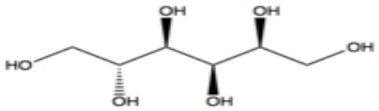
Attribute	Peripheral (PTA)
Model Number	9004
Catheter Configuration	Over-the-Wire (OTW)
Available Balloon Diameters	4.0, 5.0, 6.0 mm
Available Balloon Lengths	40, 60, 80, 100 mm
Effective Catheter Length	75, 100, 130 cm
Radiopaque Marker Bands	2
Nominal Balloon Pressure	6 atm
Balloon Rated Burst Pressure	12 atm
Maximum Guidewire	0.035"
Minimum Introducer Sheath	5F for 4.0 – 5.0 mm diameter balloon 6F for 6.0 mm diameter balloon
Coating Formulation	Active Pharmaceutical Ingredient: Paclitaxel Excipients: polysorbate, sorbitol

1.2 Drug Component Description

The active ingredient on the LUTONIX® 035 Drug Coated Balloon PTA Catheter is paclitaxel. Paclitaxel is a white powder, manufactured by a semi-synthetic process, with the empirical formula $C_{47}H_{51}NO_{14}$ and a molecular weight of 854. It is highly lipophilic, insoluble in water, and melts at approximately 216-217°C. The chemical name for paclitaxel is 5β,20-Epoxy-1,7β-dihydroxy-9-oxotax-11-ene-2α,4,10β,13α-tetrayl 4,10-diacetate 2-benzoate 13-[(2R,3S)-3-(benzoylamino)-2-hydroxy-3-phenylpropanoate]. Paclitaxel CAS Registry number is 33069-62-4. Paclitaxel has the following chemical structure:



The drug coating is a non-polymer based formulation, consisting of paclitaxel as the active pharmaceutical ingredient and polysorbate and sorbitol, inactive ingredients, which act as the drug carrier. The chemical structure of polysorbate and sorbitol are shown below:

Polysorbate	Sorbitol
	

The paclitaxel coating is evenly distributed across the working length of the balloon at a surface concentration of 2 µg/mm^2 see **Figure 2**. The key functional characteristic of the formulation is to allow for release of paclitaxel to the tissue of the vascular wall during inflation.

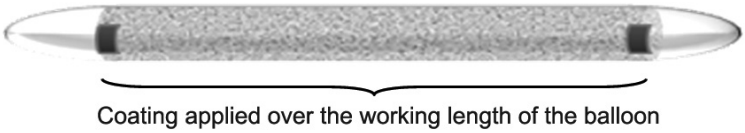


Figure 2. Drug Coating Distribution

Table 2 presents the balloon sizes and the nominal total quantity of paclitaxel on each balloon based on the surface concentration of 2 µg/mm^2.

Table 2. Balloon sizes and Paclitaxel dosage (mg)

Balloon Diameter (mm)	Total Dosage (mg) per Respective Balloon Length			
	40 mm	60 mm	80 mm	100 mm
4.0	1.0	1.5	2.0	2.5
5.0	1.3	1.9	2.5	3.1
6.0	1.5	2.3	3.0	3.8

2 INDICATIONS FOR USE

The LUTONIX® 035 Drug Coated Balloon PTA Catheter is indicated for improving luminal diameter for the treatment of obstructive de novo or non-stented restenotic lesions (≤ 15 cm in length) in native femoropopliteal arteries with reference vessel diameters of 4 mm to 6 mm.

3 CONTRAINDICATIONS

The LUTONIX® Catheter is contraindicated for use in:

- Patients with known hypersensitivity to paclitaxel or paclitaxel related compounds.
- Patients who cannot receive recommended anti-platelet and/or anticoagulant therapy.
- Women who are breastfeeding, pregnant or are intending to become pregnant or men intending to father children. It is unknown whether paclitaxel will be excreted in human milk and there is a potential for adverse reaction in nursing infants from paclitaxel exposure.

4 WARNINGS

- Contents supplied STERILE using ethylene oxide (EO) process. Do not use if sterile barrier is damaged or opened prior to intended use.
- Do not use if product damage is evident.
- The LUTONIX® Catheter is for use in one patient only; do not reuse in another patient, reprocess or resterilize. Risks of reuse in another patient, reprocessing, or resterilization include:
  - Compromising the structural integrity of the device and/or device failure which, in turn, may result in patient injury, illness or death.
  - Creating a risk of device contamination and/or patient infection or cross-infection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to patient injury, illness or death.
- Do not exceed the Rated Burst Pressure (RBP) recommended for this device. Balloon rupture may occur if the RBP rating is exceeded. To prevent over-pressurization, use of a pressure monitoring device is recommended.
- Use the recommended balloon inflation medium of contrast and sterile saline (≤50% contrast). Never use air or any gaseous medium to inflate the balloon.

5 PRECAUTIONS

5.1 General Precautions

- The LUTONIX® Catheter should only be used by physicians trained in percutaneous interventional procedures.
- The safety and effectiveness of the Lutonix® Catheter have not been established in pediatric patients and in adult cerebral, carotid, or renal vasculature.
- Consideration should be given to the risks and benefits of use in patients with a history of non-controllable allergies to contrast agents.
- Use of more than two LUTONIX® Catheters deployed in a single target lesion during a single procedure has not been assessed.

5.2 Use in Conjunction with Other Procedures

It is not recommended that the LUTONIX® Catheter be used in conjunction with other drug coated balloons or drug eluting stents to treat the same lesion in the same procedure or within 90 days. The safety of combinations of different drug-device products has not been assessed.

5.3 Use in Special Populations

- Pregnancy – Use in women who are breastfeeding, pregnant or intending to become pregnant or in men intending to father children is contraindicated.
- Pediatric Use – The safety and effectiveness of the LUTONIX® Catheter in pediatric patients has not been established.
- Geriatric Use – Clinical studies of the LUTONIX® Catheter did not have an upper age limit.

5.4 Device Handling Precautions

- Do not immerse the LUTONIX® Catheter in a saline bath. Replace any device where the balloon has come into contact with fluids prior to use.
- The coated balloon portion should be handled with dry sterile gloves whenever possible prior to use. Care should be taken to minimize unnecessary contact with the coated balloon portion of the LUTONIX® Catheter during preparation and insertion.
- The balloon protector and wire lumen stylet should stay in place during preparation of the LUTONIX® Catheter and not be removed until just prior to placing over guidewire.
- If difficulty is encountered while removing the balloon protector after flexing, a new LUTONIX® Catheter shall be utilized.

5.5 Device Use/Procedure Precautions

- To ensure therapeutic drug delivery:
  - Never inflate the LUTONIX® Drug Coated Balloon prior to reaching the target lesion.
  - The LUTONIX® Catheter should be advanced to the target site in an efficient manner (≤ 3 minutes) and immediately inflated.
  - Maintain balloon inflation for a minimum of 30 seconds. Use the maximum balloon inflation time per your institution's standard of care.
- For optimal results, predilatation smaller than the reference vessel diameter is recommended for highly stenosed, calcified or difficult to cross lesions.

- After insertion, do not over-tighten the hemostatic adaptor (if used) around the LUTONIX® Catheter shaft as lumen constriction may occur, affecting inflation/deflation of the balloon.
- Always advance and retrieve the LUTONIX® Catheter under negative pressure.
- The LUTONIX® Catheter should always be manipulated under fluoroscopic observation when in the body.
- Do not continue to use the LUTONIX® Catheter if the shaft has been bent or kinked.
- Whenever possible, the LUTONIX® Catheter should be the final treatment of the vessel; however, post-dilatation is allowed with other PTA catheter or used LUTONIX® catheter.

5.6 Pre- and Post-Procedure Antiplatelet Regimen

Dual antiplatelet therapy should be administered according to current medical standards pre-procedure and for a minimum of 4 weeks after the intervention. Prolonged antiplatelet therapy can be given at the discretion of the physician.

6 DRUG INFORMATION

6.1 Mechanism of Action

The mechanism by which the LUTONIX® Catheter inhibits neointimal growth as seen in preclinical and clinical studies has not been established. The LUTONIX® Catheter coating contains paclitaxel, an anti-proliferative pharmaceutical agent that specifically binds to and stabilizes microtubules. By blocking microtubule depolymerization, paclitaxel affects inhibition of smooth muscle cell and fibroblast proliferation and migration as well as secretion of extracellular matrix. The combination of these effects results in the inhibition of neointimal hyperplasia and therefore preventing restenosis.

6.2 Pharmacokinetics

The pharmacokinetics of paclitaxel following treatment with the LUTONIX® Catheter was evaluated in a subset of patients randomized to the LUTONIX® Catheter arm in the LEVANT 2 clinical study who received varied doses in the 1.3 mg – 5 mg range (n=22 subjects). All subjects had detectable serum paclitaxel immediately after the index procedure that decreased to less than 3 ng/mL within one hour. The pharmacokinetics of paclitaxel following treatment generally exhibited a bi-exponential decay; characterized by a rapid distribution phase followed by a log-linear elimination phase. Group mean (SD) values for the pharmacokinetic parameters C_{max}, AUC_{all}, and MRT_{last} were 5.10 (3.21) ng/mL, 8.39 (4.00) ng*h/mL, and 2.13 (1.84) h.

6.3 Drug Interactions

Formal drug interaction studies have not been conducted with the LUTONIX® Catheter, and therefore the instruction for use of all treatment-accompanying drugs should be consulted for interactions with paclitaxel. Consideration should be given to the potential for both systemic and local drug interactions in the vessel wall when deciding to use the LUTONIX® Catheter in a patient who is taking a drug with known interaction to paclitaxel or when deciding to initiate therapy with such a drug in a patient who has recently undergone a procedure with a LUTONIX® Catheter. The metabolism of paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4, and it is a substrate of P-glycoprotein. Potential drug interactions may occur with any drug that affects these isoenzymes. In the absence of formal clinical drug interaction studies, caution should be exercised when administering paclitaxel concomitantly with known substrates or inhibitors of the cytochrome P450 isoenzymes CYP2C8 and CYP3A4.

6.4 Carcinogenicity, Genotoxicity, and Reproductive Toxicology

No long-term studies in animals have been performed to evaluate the carcinogenic potential of the drug paclitaxel or of the LUTONIX® Catheter, and there are no adequate and well-controlled studies published in pregnant women or in men intending to father children. Paclitaxel inhibits cell proliferation by interacting with microtubules, and one consequence is the loss of whole chromosomes during cell division. This indirect action is consistent with positive responses in vitro and in vivo micronucleus genotoxitiy assays, which detect DNA fragments. Positive results have also been reported for chromosomal aberrations in primary human lymphocytes. It is not known whether paclitaxel has a separate direct action on DNA in the generation of DNA strand breaks or fragments. It is negative in assays for gene mutation, including salmonella and CHO/HPRT.

Studies performed in rat and rabbits receiving IV paclitaxel during organogenesis revealed evidence of maternal toxicity, embryotoxicity, and fetotoxicity at dosages of 1 and 3 mg/kg, respectively (approximately 3 and 16 times the dose provided by the LUTONIX® Catheter coated with 3.8 mg paclitaxel (6mm x 100mm balloon) adjusted for body surface area). The drug resulted in increased resorptions and increased fetal deaths. No teratogenicity was observed in gravid rats receiving daily IV paclitaxel doses of 1 mg/kg (a daily dose of approximately 3 times the dose of the LUTONIX® Catheter (6mm x 100mm), adjusted for body surface area).

The treating physician should balance the potential medical benefits of the LUTONIX® Catheter against these genotoxic and reproductive risks.

7 POTENTIAL ADVERSE EVENTS

Potential adverse events which may be associated with a peripheral balloon dilatation procedure include:

- Additional intervention
- Allergic reaction to drugs or contrast medium
- Aneurysm or pseudoaneurysm
- Arrythmias
- Embolization
- Hematoma
- Hemorrhage, including bleeding at the puncture site
- Hypotension/hypertension
- Inflammation
- Occlusion
- Pain or tenderness
- Pneumothorax or hemothorax
- Sepsis/infection
- Shock
- Stroke
- Thrombosis
- Vessel dissection, perforation, rupture, or spasm

Although system effects are not anticipated, refer to the Physicians' Desk Reference for more information on the potential adverse events observed with paclitaxel.

Potential adverse events not indicated above, that may be unique to the Lutonix® Catheter paclitaxel drug coating:

- Allergic/immunologic reaction to drug coating

There may be other potential adverse events that are unforeseen at this time. The list of adverse events observed during the LEVANT 2 clinical study is provided it **Table 13** below.

8 PATIENT COUNSELING INFORMATION

Physicians should consider the following in counseling patients about this product:

- Discuss the risks associated with a PTA procedure
- Discuss the risks associated with a paclitaxel coated PTA catheter
- Discuss the risks/benefits issues for this particular patient
- Post-procedure antithrombotic regimen
- Discuss alteration to current lifestyle immediately following the procedure and over the long term

9 CLINICAL STUDIES

The safety and effectiveness of the LUTONIX® Catheter is derived from and the LEVANT 2 multicenter randomized pivotal IDE trial and the LEVANT I multicenter randomized European trial.

The one year results from the LEVANT 2 pivotal trial and the two-year final results from the LEVANT 1 trial are presented below. Patient follow-up for the LEVANT 2 trial is planned out to 5-years and is ongoing.

9.1 LEVANT 2 Randomized Pivotal Trial

9.1.1 Study Design

The LEVANT 2 Randomized clinical trial is a prospective, multicenter, single blind, randomized, controlled trial comparing the LUTONIX 035 Drug Coated Balloon PTA Catheter vs. standard balloon angioplasty for treatment of de novo or non-stented restenotic lesions in native femoropopliteal arteries.

The LEVANT 2 Randomized clinical trial recruited patients with denovo or restenotic lesion in the femoropopliteal artery. After baseline angiogram and protocol-defined pre-dilatation, subjects who were likely to have successful revascularization using PTA balloon (i.e. were unlikely to require a stent) were randomized 2:1 to treatment with either the LUTONIX 035 Drug Coated Balloon PTA Catheter (Test Arm) or standard PTA catheter (Control Arm). Subjects who did not meet the protocol-defined criteria after pre-dilatation were treated per standard practice and followed for safety through 30 days.

Overview of the study flowchart is provided in the **Figure 3** and the overview of the LEVANT 2 study design if provided in **Table 3** below.

Figure 3: Study Flow Chart

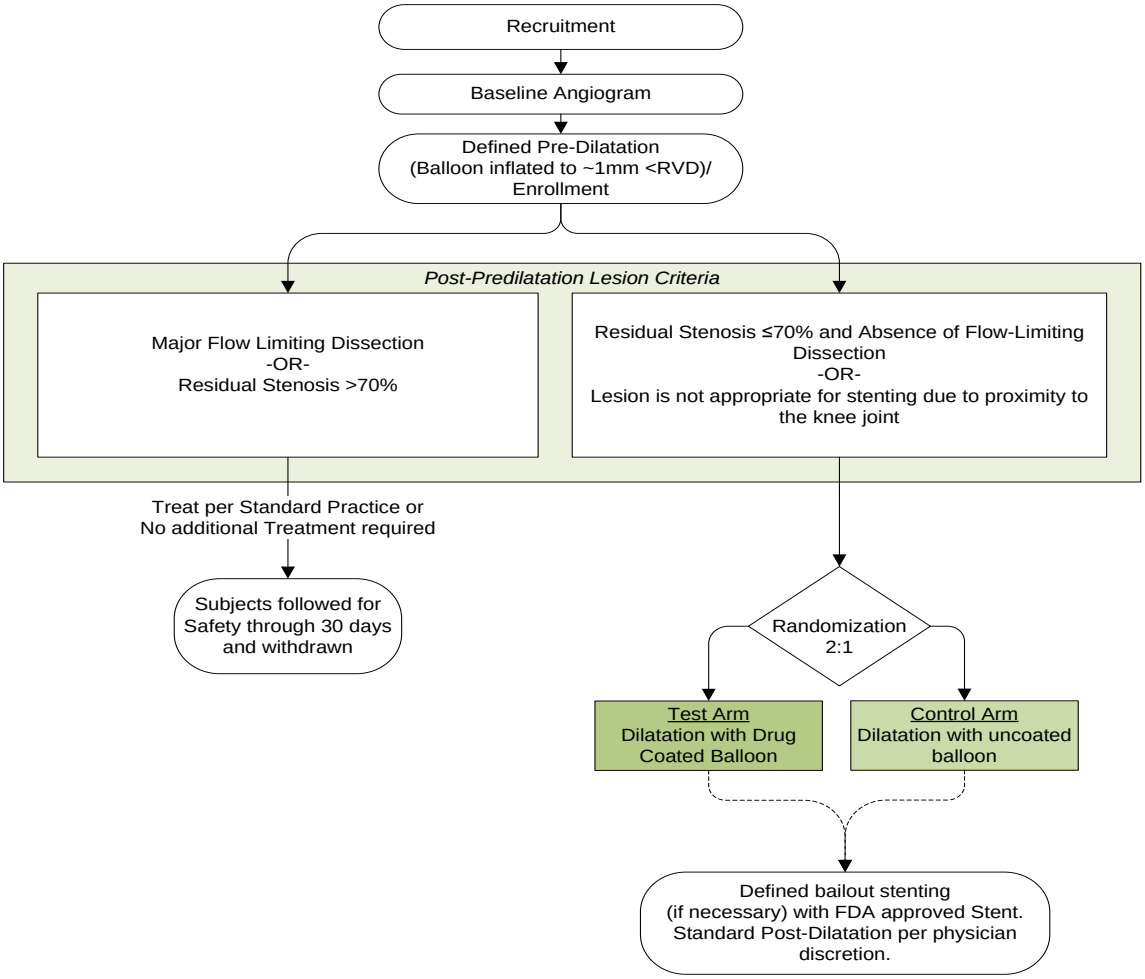
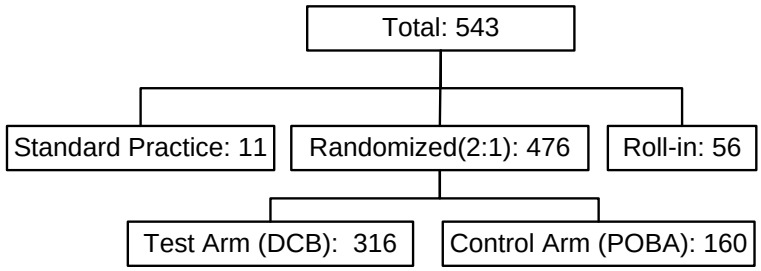


Table 3. LEVANT 2 Randomized Clinical Trial Study Design

Item	Description
Study Type/Design	Prospective, Multicenter, Single Blind, Randomized, Safety and Efficacy
Number of Subjects Enrolled	
Treatment Lesion	De novo or restenotic angiographically significant lesion in the superficial femoral or popliteal artery with lesion length of ≤ 15 cm in length and reference vessel of 4 mm – 6 mm in diameter.
Treatment Device	Test Arm: Lutonix 035 Drug Coated Balloon PTA Catheter (formerly known as Moxy Drug Coated Balloon) Control Arm: Non-coated standard percutaneous transluminal angioplasty balloon catheter (standard PTA catheter)
Balloon Sizes	Balloon Diameters: 4 mm, 5 mm, & 6 mm Balloon Lengths: 40 mm, 60 mm and 100 mm in length.
Concomitant Medication	Appropriate antiplatelet therapy (clopidogrel or prasugrel) for at least 1 month and aspirin indefinitely. Anticoagulation was per hospital standard practice.
Primary Endpoints	<u>Safety</u> Composite of freedom from all-cause perioperative (≤30 day) death and freedom at 1 year from the following: index limb amputation (above or below the ankle), index limb re-intervention, and index-limb-related death. <u>Efficacy</u> Primary Patency of the target lesion at 1 year. Primary Patency is defined as the absence of target lesion restenosis (as adjudicated by blinded core-lab) and freedom from target lesion revascularization (TLR).
Randomized Subject Follow-Up Schedule	*Clinical*: 6, 12, and 24 Months *Duplex Ultrasound (DUS):* 0-30 days, 6 months, 12 months, and 24 months *Telephone:* 1, 36, 48 and 60 Months
PK Study	Pharmacokinetic testing for up to 30-days from up to 30 subjects treated with the Lutonix DCB.
Status	One year results reported

9.1.2 Clinical Inclusion/Exclusion Criteria

Enrollment in the LEVANT 2 Randomized clinical trial was limited to subjects who met the eligibility criteria and who provided a signed informed consent form prior to enrollment. Subjects had to be at least 18 years old, be presenting with claudication or ischemic rest pain, have an angiographically significant lesion in the femoropopliteal artery, and have an outflow artery to the foot. Female subjects with childbearing potential had to have a negative pregnancy test within 30-days of the index procedure.

Clinical Inclusion Criteria

1. Male or non-pregnant female ≥18 years of age;
2. Rutherford Clinical Category 2-4;
3. Subject is willing to provide informed consent, is geographically stable and comply with the required follow up visits, testing schedule and medication regimen;

Angiographic Inclusion Criteria

1. Lesion Length ≤15 cm;
2. Up to two focal lesions or segments within the designated 15 cm length of vessel may be treated (e.g. two discrete segments, separated by several cm, but both falling within a composite length of ≤15 cm);
3. ≥70% stenosis by visual estimate;
4. Lesion location starts ≥1 cm below the common femoral bifurcation and terminates distally ≤2 cm below the tibial plateau AND ≥1 cm above the origin of the TP trunk;
5. *de novo* lesion(s) or non-stented restenotic lesion(s) >90 days from prior angioplasty procedure
6. Lesion is located at least 3 cm from any stent, if target vessel was previously stented;
7. Target vessel diameter between ≥4 and ≤6 mm and able to be treated with available device size matrix;
8. Successful, uncomplicated (without use of a crossing device) antegrade wire crossing of lesion;
9. A patent inflow artery free from significant lesion (≥50% stenosis) as confirmed by angiography (treatment of target lesion acceptable after successful treatment of inflow artery lesions);
   NOTE: Successful inflow artery treatment is defined as attainment of residual diameter stenosis ≤30% without death or major vascular complication.
10. At least one patent native outflow artery to the ankle, free from significant (≥50%) stenosis as confirmed by angiography that has not previously been revascularized (treatment of outflow disease is NOT permitted during the index procedure);
11. Contralateral limb lesion(s) cannot be treated within 2 weeks before and/or planned 30 days after the protocol treatment in order to avoid confounding complications;
12. No other prior vascular interventions within 2 weeks before and/or planned 30 days after the protocol treatment.

Exclusion Criteria:

1. Pregnant or planning on becoming pregnant or men intending to father children;

2. Life expectancy of <5 years;
3. Patient is currently participating in an investigational drug or other device study or previously enrolled in this study;

   NOTE: Enrollment in another clinical trial during the follow up period is not allowed.
4. History of hemorrhagic stroke within 3 months;
5. Previous or planned surgical or interventional procedure within 2 weeks before or within 30 days after the index procedure;
6. History of MI, thrombolysis or angina within 2 weeks of enrollment;
7. Rutherford Class 0, 1, 5 or 6;
8. Renal failure or chronic kidney disease with MDRD GFR ≤30 ml/min per 1.73 m^2 (or serum creatinine ≥2.5 mg/L within 30 days of index procedure or treated with dialysis);
9. Prior vascular surgery of the index limb, with the exception of remote common femoral patch angioplasty separated by at least 2 cm from the target lesion;
10. Inability to take required study medications or allergy to contrast that cannot be adequately managed with pre- and post-procedure medication;
11. Anticipated use of IIb/IIIa inhibitor prior to randomization;
12. Ipsilateral retrograde access;
13. Composite lesion length is >15 cm or there is no normal proximal arterial segment in which duplex flow velocity can be measured;
14. Significant inflow disease. Successful treatment of inflow disease allowed prior to target lesion treatment;
15. Known inadequate distal outflow (>50% stenosis of distal popliteal and/or all three tibial vessels), or planned future treatment of vascular disease distal to the target lesion;
16. Sudden symptom onset, acute vessel occlusion, or acute or sub-acute thrombus in target vessel;
17. Severe calcification that renders the lesion undilatable;
18. Use of adjunctive primary treatment modalities (i.e. laser, atherectomy, cryoplasty, scoring/cutting balloon, etc.).

9.1.3 Clinical Primary Endpoints

The primary efficacy endpoint for the LEVANT 2 Randomized clinical trial is primary patency of the target lesion at 1 year with primary patency defined as:

- Absence of target lesion restenosis (as adjudicated by blinded core-lab), and
- Freedom from target lesion revascularization (TLR).

The primary safety endpoint is the composite of freedom from all-cause perioperative (≤30 day) death and freedom at 1 year from the following:

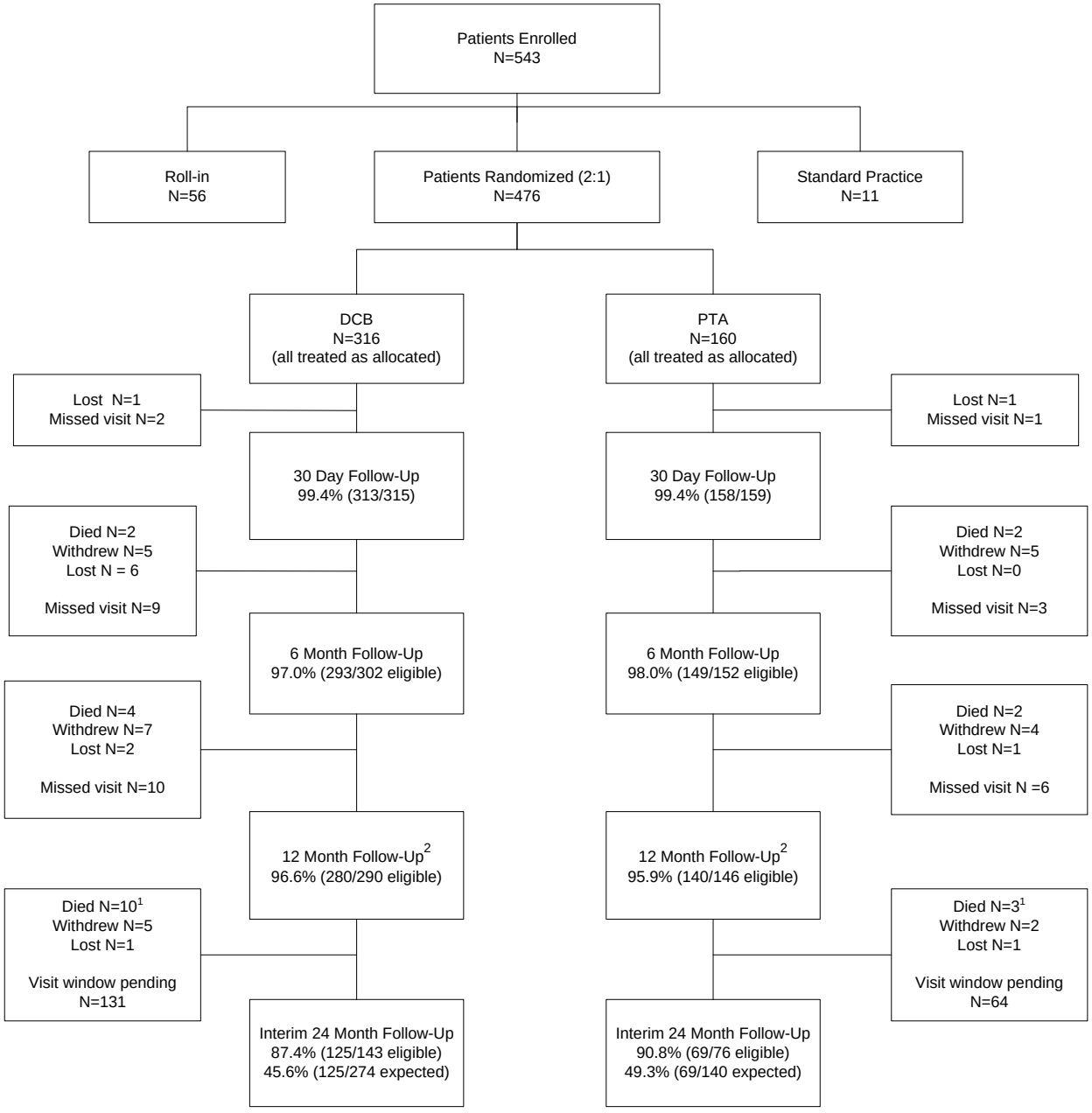
- Index limb amputation (above or below the ankle),
- Index limb re-intervention, and
- Index-limb-related death.

9.1.4 Accountability of Subjects

Five hundred forty-three (543) subjects were enrolled into the LEVANT 2 Randomized clinical trial of which four hundred seventy-six (n=476) subjects were randomized 2:1 to Lutonix Drug Coated Balloon (n=316) and PTA (n=160). Fifty-six (56) subjects were roll-in subjects and treated with Lutonix DCB (53 as site training cases and 3 as live-cases in Europe). Eleven (11) subjects did not meet the post pre-dilatation inclusion criteria and were treated per standard practice and followed for safety only for 30 days. Reference **Figure 4** for the LEVANT 2 subject enrollment.

At the time of database lock on Feb 26, 2014, of the 476 randomized subjects enrolled and per intent-to-treat (ITT) analysis, 471 subjects (98.9% ITT) completed the 30-day follow-up; 442 subjects (92.9% ITT) completed the 6-month follow-up, and 420 subjects (88.2% ITT) completed the 12-month follow-up. Reference **Table 4** for the subject disposition and **Table 5** for subject disposition of evaluable subjects for primary endpoint analyses.

Figure 4. LEVANT 2 Subjects Enrolled



[1] One DCB subject died within the 12-month follow-up window after a 12-month follow-visit and is shown as exiting between 12 and 24 months. Deaths between 12 and 24 months include (n =6 DCB vs 2 PTA) that have not yet been CEC adjudicated. Exit reason "other" (n=2 vs. 1) are included as lost.

[2] Telephone contact with family/physicians was obtained for two patients (1 DCB and 1 PTA) exiting in the 12 month window; these are included in the Consort diagram **Figure 3** as exiting between 12 and 24 months.

Table 4. Subject Disposition

Variable	Test DCB (N=316)	Control PTA (N=160)
Roll-in, N	56	0
ITT (Randomized), N	316	160
As-Treated, N	316	160
Per-Protocol, N	291	122
Follow-up Information Obtained (ITT)		
1-Month[1]	99.1% (313/316)	98.8% (158/160)
Clinical visit completed[1]	50.0% (158/316)	49.4% (79/160)
6-Month[2]	92.7% (293/316)	93.1% (149/160)
Clinical visit completed	90.8% (287/316)	91.3% (146/160)
Analyzable DUS	74.1% (234/316)	75.6% (121/160)
12-Month[3]	88.6% (280/316)	87.5% (140/160)
Clinical visit completed	85.1% (269/316)	84.4% (135/160)
Analyzable DUS	74.4% (235/316)	68.8% (110/160)
24-Month	39.6% (125/316)	43.1% (69/160)
Clinical visit completed	38.3% (121/316)	41.9% (67/160)
Analyzable DUS	25.0% (79/316)	23.8% (38/160)
Discontinuation Reasons (ITT)		
Subject died[4]	5.1% (16/316)	4.4% (7/160)
Subject refused further participation	5.7% (18/316)	6.9% (11/160)
Subject is lost to follow-up	2.5% (8/316)	1.3% (2/160)
Other[5]	0.6% (2/316)	0.6% (1/160)

[1] One-month visit could also be completed via telephone (49.7% test DCB, 50.3% control PTA).
[2] Information obtained by telephone for 6 (1.9%) test and 3 (1.9%) control subjects with missed visits.
[3] Information obtained by telephone for 11 (3.5%) test and 5 (3.1%) control subjects with missed visits.
[4] Includes 6 test and 2 control deaths between 12 and 24 months include that have not yet been CEC adjudicated.
[5] Discontinuation Reason "Other" is included as "lost" in the Consort Flow Diagram (Figure 3 above).

Table 5. Evaluable Subjects for Primary Endpoint Analyses (ITT Population)

Information Source	Test DCB	Control PTA
Analyzable for 12 month Primary Efficacy Endpoint (Primary Patency)	**83.5% (264/316)**	**84.4% (135/160)**
In-window Clinical Visit with analyzable DUS Completed, without TLR prior to end of 12m window	64.6% (204/316)	58.1% (93/160)
TLR prior to end of 12m window	11.1% (35/316)	15.0% (24/160)
Binary restenosis adjudicated on most recent prior DUS without TLR or evaluable 12m DUS	3.5% (11/316)	6.3% (10/160)
Freedom from TLR and absence of binary restenosis determined by subsequent visit with analyzable DUS	4.4% (14/316)	5.0% (8/160)
Analyzable for 12 month Primary Safety Endpoint	**90.5% (286/316)**	**89.4% (143/160)**
In-window Clinical Visit and/or failed prior to 395 days	81.0% (256/316)	78.8% (126/160)
Freedom from safety events through 395 days demonstrated by subsequent contact	9.5% (30/316)	10.6% (17/160)

9.1.5 Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a peripheral arterial disease study performed in the US and the baseline patient characteristics were similar between the Lutonix DCB and PTA control treatment groups.

Demographics (**Table 6**), medical history (**Table 7**) and clinical characteristics (**Table 8**) were similar for the two treatment groups. There were similar frequency of diabetes treated in both groups (43.4% vs. 41.9%), although a higher percentage of these were Type I for the Lutonix DCB arm (9.5% vs. 1.5%, p=0.03), and there was a similar frequency of prior stroke (11.4% vs. 11.3%), although a lower percentage of these were ischemic in the Lutonix DCB arm (75% vs. 100%, p=0.02). Overall, comorbidities at baseline was well-matched and representative of the patient population with peripheral vascular disease.

Similarly, baseline angiographic data (**Table 9**) indicate that the Lutonix DCB and control PTA subjects were well-balanced with respect to lesions treated, lesion length, diameter of stenosis, lesion class, classification, occlusion, location, and other lesion-specific measures.

Table 6. Demographics

Variable	Test DCB	Control PTA	P-value[1]	Pooled
Age (years), Mean ± SD (n) median (min, max)	67.8 ± 10.0 (316) 68.2 (44.5, 91.4)	69.0 ± 9.0 (160) 69.0 (41.5, 89.4)	0.209	68.2 ± 9.7 (476) 68.4 (41.5, 91.4)
Gender, % (n/N)			0.216	
Female	38.9% (123/316)	33.1% (53/160)		37.0% (176/476)
Male	61.1% (193/316)	66.9% (107/160)		63.0% (300/476)
Ethnicity, % (n/N)			0.741	
Hispanic or Latino	7.9% (25/316)	8.8% (14/160)		8.2% (39/476)
Not Hispanic or Latino	91.8% (290/316)	91.3% (146/160)		91.6% (436/476)
Patient chose not to respond	0.3% (1/316)	0.0% (0/160)		0.2% (1/476)
Race, % (n/N)			0.160	
Asian	1.3% (4/316)	2.5% (4/160)		1.7% (8/476)
Black or African American	3.8% (12/316)	8.1% (13/160)		5.3% (25/476)
Patient chose not to respond	4.1% (13/316)	4.4% (7/160)		4.2% (20/476)
White	90.8% (287/316)	85.0% (136/160)		88.9% (423/476)
Height (cm), Mean ± SD (n) median (min, max)	169.3 ± 10.3 (316) 170.0 (135.0, 194.0)	170.3 ± 10.1 (160) 171.5 (142.0, 190.0)	0.335	169.6 ± 10.2 (476) 170.0 (135.0, 194.0)
Weight (kg), Mean ± SD (n) median (min, max)	83.1 ± 17.0 (316) 82.0 (42.0, 146.0)	82.5 ± 17.1 (160) 80.0 (48.0, 133.0)	0.709	82.9 ± 17.0 (476) 82.0 (42.0, 146.0)
BMI (kg/m^2), Mean ± SD (n) median (min, max)	29.0 ± 5.3 (316) 28.5 (15.8, 52.7)	28.3 ± 4.8 (160) 27.9 (18.1, 48.5)	0.221	28.7 ± 5.2 (476) 28.1 (15.8, 52.7)

[1] T-tests for means and X^2-tests for proportions

Table 7. Medical History

Variable	Test DCB	Control PTA	P-value[1]	Pooled
BMI>=30, % (n/N)	34.8% (110/316)	30.6% (49/160)	0.360	33.4% (159/476)
Smoking, % (n/N)			0.548	
Current smoker	35.1% (111/316)	33.8% (54/160)		34.7% (165/476)
Never smoked	20.9% (66/316)	17.5% (28/160)		19.7% (94/476)
Previously smoked	44.0% (139/316)	48.8% (78/160)		45.6% (217/476)
Dyslipidemia/Hypercholesterolemia, % (n/N)	89.6% (283/316)	86.3% (138/160)	0.286	88.4% (421/476)
Diabetes Mellitus, % (n/N)	43.4% (137/316)	41.9% (67/160)	0.758	42.9% (204/476)
Type			0.034	
Type I	9.5% (13/137)	1.5% (1/67)		6.9% (14/204)
Type II	90.5% (124/137)	98.5% (66/67)		93.1% (190/204)
Insulin Dependency	40.9% (56/137)	40.3% (27/67)	0.937	40.7% (83/204)

Variable	Test DCB	Control PTA	P-value[1]	Pooled
Hypertension, % (n/N)	89.2% (282/316)	87.5% (140/160)	0.572	88.7% (422/476)
Renal Failure, % (n/N)	3.5% (11/316)	4.4% (7/160)	0.629	3.8% (18/476)
Congestive Heart Failure, % (n/N)	5.7% (18/316)	3.1% (5/160)	0.217	4.8% (23/476)
Previous CAD, % (n/N)	49.7% (157/316)	48.1% (77/160)	0.748	49.2% (234/476)
Previous MI, % (n/N)	19.9% (63/316)	17.5% (28/160)	0.523	19.1% (91/476)
Chronic Angina, % (n/N)	4.7% (15/316)	5.0% (8/160)	0.903	4.8% (23/476)
History of Coronary Revascularization, % (n/N)	41.8% (132/316)	38.8% (62/160)	0.526	40.8% (194/476)
Type of Coronary Revascularization			0.429	
CABG	45.2% (47/104)	52.1% (25/48)		47.4% (72/152)
PCI	54.8% (57/104)	47.9% (23/48)		52.6% (80/152)
Previous Cerebrovascular Event, % (n/N)	11.4% (36/316)	11.3% (18/160)	0.963	11.3% (54/476)
Ischemic	75.0% (27/36)	100.0% (18/18)	0.020	83.3% (45/54)
Hemorrhagic	5.6% (2/36)	0.0% (0/18)	0.308	3.7% (2/54)
Previous Target Limb Intervention, % (n/N)	23.4% (74/316)	17.5% (28/160)	0.137	21.4% (102/476)
Target Vessel Type			0.292	
DeNovo Target Vessel	83.9% (265/316)	87.5% (140/160)		85.1% (405/476)
Restenosed Target Vessel	16.1% (51/316)	12.5% (20/160)		14.9% (71/476)

[1] T-tests for means and X^2-tests for proportions

Table 8. Clinical Characteristics

Variable	Test DCB	Control PTA	P-value[1]	Pooled
Rutherford Grade, % (n/N)			0.521	
2	29.4% (93/316)	34.4% (55/160)		31.1% (148/476)
3	62.7% (198/316)	57.5% (92/160)		60.9% (290/476)
4	7.9% (25/316)	8.1% (13/160)		8.0% (38/476)
ABI of Target Limb[2], Mean ± SD (n) median (min, max)	0.74 ± 0.20 (306) 0.73 (0.00, 1.38)	0.73 ± 0.18 (156) 0.73 (0.00, 1.17)	0.467	0.74 ± 0.20 (462) 0.73 (0.00, 1.38)
ABI of Contralateral Limb, Mean ± SD (n) median (min, max)	0.87 ± 0.23 (301) 0.92 (0.00, 1.34)	0.87 ± 0.20 (152) 0.89 (0.00, 1.30)	0.783	0.87 ± 0.22 (453) 0.91 (0.00, 1.34)

[1] T-tests for means and X2-tests for proportions
[2] Pressures > 1.4 were excluded from this analysis (n = 3 for Lutonix DCB, n = 1 for control PTA) per the Measurement and Interpretation of the Ankle-Brachial Index guidelines from the American Heart Association.

Table 9. Baseline Angiographic Data

Variable[1]	Test DCB	Control PTA	P-value[2]	Pooled
Number of Lesions Treated, % (n/N)			0.400	
1	98.1% (310/316)	96.9% (155/160)		97.7% (465/476)
2	1.9% (6/316)	3.1% (5/160)		2.3% (11/476)
Total Target Lesion Length (mm, core lab), Mean ± SD (n) median (min, max)	62.7 ± 41.4 (315) 51.5 (5.7, 196.7)	63.2 ± 40.4 (160) 51.8 (7.5, 173.7)	0.900	62.8 ± 41.0 (475) 51.6 (5.7, 196.7)
Total Target Lesion Length (mm, site), Mean ± SD (n) median (min, max)	69.6 ± 43.8 (316) 70.0 (1.0, 150.0)	69.6 ± 43.9 (160) 70.0 (2.0, 150.0)	0.987	69.6 ± 43.8 (476) 70.0 (1.0, 150.0)
Treated Length (mm), Mean ± SD (n) median (min, max)	107.9 ± 47.0 (316) 105.3 (29.9, 233.9)	107.9 ± 49.4 (160) 103.4 (23.3, 307.7)	0.988	107.9 ± 47.8 (476) 104.9 (23.3, 307.7)
Maximum Percent Stenosis, %DS, Mean ± SD (n) median (min, max)	80.5 ± 14.8 (316) 81.0 (40.0, 100.0)	80.9 ± 14.9 (160) 82.0 (45.0, 100.0)	0.776	80.6 ± 14.8 (476) 81.0 (40.0, 100.0)
Average RVD (mm), Mean ± SD (n) median (min, max)	4.8 ± 0.8 (316) 4.7 (3.0, 7.5)	4.8 ± 0.8 (160) 4.7 (2.8, 7.1)	0.981	4.8 ± 0.8 (476) 4.7 (2.8, 7.5)
Target Limb, % (n/N)			0.841	
Left	52.8% (167/316)	51.9% (83/160)		52.5% (250/476)
Right	47.2% (149/316)	48.1% (77/160)		47.5% (226/476)
Lesion Class TASC II, % (n/N)			0.398	
A	76.3% (241/316)	75.6% (121/160)		76.1% (362/476)
B	21.5% (68/316)	23.8% (38/160)		22.3% (106/476)
C	2.2% (7/316)	0.6% (1/160)		1.7% (8/476)
Calcification, % (n/N)	59.2% (187/316)	58.1% (93/160)	0.826	58.8% (280/476)
Severe Calcification	10.4% (33/316)	8.1% (13/160)	0.419	9.7% (46/476)
Total Occlusion, % (n/N)	20.6% (65/316)	21.9% (35/160)	0.741	21.0% (100/476)
Number of Patent Run-Off Vessels, Mean ± SD (n) median (min, max)	2.1 ± 1.0 (316) 2.0 (0.0, 3.0)	1.9 ± 1.0 (160) 2.0 (0.0, 3.0)	0.148	2.0 ± 1.0 (476) 2.0 (0.0, 3.0)
Number of Patent Run-Off Vessels (Categorical), % (n/N)			0.539	
0	9.5% (30/316)	13.1% (21/160)		10.7% (51/476)
1	15.2% (48/316)	16.9% (27/160)		15.8% (75/476)
2	35.4% (112/316)	35.0% (56/160)		35.3% (168/476)
3	39.9% (126/316)	35.0% (56/160)		38.2% (182/476)

Variable[1]	Test DCB	Control PTA	P-value[2]	Pooled
Most Distal Lesion Location, % (n/N)			0.495	
Proximal SFA	9.2% (29/316)	8.1% (13/160)		8.8% (42/476)
Mid SFA	51.3% (162/316)	45.6% (73/160)		49.4% (235/476)
Distal SFA	29.7% (94/316)	38.8% (62/160)		32.8% (156/476)
Proximal Popliteal	4.7% (15/316)	4.4% (7/160)		4.6% (22/476)
Mid Popliteal	4.1% (13/316)	2.5% (4/160)		3.6% (17/476)
Distal Popliteal	0.9% (3/316)	0.6% (1/160)		0.8% (4/476)
Most Distal Lesion Location Rank[3], Mean ± SD (n) median (min, max)	2.46 ± 0.94 (316) 2.00 (1.00, 6.00)	2.49 ± 0.85 (160) 2.00 (1.00, 6.00)	0.721	2.47 ± 0.91 (476) 2.00 (1.00, 6.00)

[1]All values per angiographic core lab except where indicated
[2] T-tests for means and X^2-tests for proportions
[3] Lesion locations are ranked 1-6 from least to most distal, in the order displayed.

9.1.6 Safety and Effectiveness Results

9.1.6.1 Primary Safety Endpoint

The primary safety endpoint was the composite of freedom from all-cause perioperative (≤30 day) death and freedom at 1 year from index limb amputation (above or below the ankle), index limb re-intervention, and index-limb-related death.

Overall, 90.5% (286/316) Lutonix DCB subjects and 89.4% (143/160) control PTA subjects were evaluable for primary safety endpoint testing. Missing subjects included 7.3% (23) Lutonix DCB and 8.1% (13) control PTA subjects who either died, withdrew, or were lost-to-follow-up without prior safety events and 2.2% (7) Lutonix DCB and 2.5% (4) control PTA subjects with missed visits at 12 month and had no prior safety events or later evidence of success.

The proportion of subjects that had freedom from any safety events in the Lutonix DCB group was 83.9% compared to 79.0% in the standard PTA group at 12 months, and non-inferior safety was demonstrated (p = 0.005) with a non-inferiority margin of 5% - see **Table 10**.

Table 10. Primary Safety Endpoint at 1 year (ITT Population)

Measure	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference % [95% CI]	P-value[2]
Freedom from Primary Safety Event[1]	83.9% (240/286) [79.7, 88.2]	79.0% (113/143) [72.3, 85.7]	4.9% [-2.6, 12.3]	0.005

[1] Composite freedom from safety events, including all-cause perioperative (≤30 day) death, index limb amputation (above or below the ankle), index limb re-intervention, or index-limb-related death.
[2] P-value and CI for difference based on a Farrington-Manning method. Confidence intervals for groups are asymptotic. Margin of non-inferiority 5%.

Table 11. Safety Events through 1 year (ITT Population)

Safety Event *(subject may have more than one event)*	**Test DCB %(n/N) [95% CI]**	**Control PTA %(n/N) [95% CI]**	**Difference[1] % [95% CI]**
Perioperative (≤30) Death	0.0% (0/308) [0.0, 0.0]	0.0% (0/155) [0.0, 0.0]	0.0%
Index Limb Related Death at 12 Months	0.0% (0/285) [0.0, 0.0]	0.0% (0/140) [0.0, 0.0]	0.0%
Amputation at 12 Months	0.3% (1/286) [0.0, 1.0]	0.0% (0/140) [0.0, 0.0]	0.3% [-0.3, 1.0]
Target Limb Revascularization 12 months	15.4% (44/285) [11.2, 19.6]	21.0% (30/143) [14.3, 27.7]	-5.5% [-13.4, 2.3]

[1] Nominal CI for difference based on a Farrington-Manning method are provided but were not prespecified for hypothesis testing and are not adjusted for multiplicity. CI for groups are asymptotic.

Kaplan-Meier survival analysis

The primary safety endpoint was also analyzed using time-to-event Kaplan-Meier survival analysis as one of the sensitivity analyses to address the issue of missing data.

Kaplan-Meier analysis confirmed the safety of the Lutonix DCB compared to control PTA through 1 year (**Figure 5** and **Table 12**). At 365 days, 86.7% of Lutonix DCB subjects and 81.5% of standard PTA subjects were free from safety events.

Figure 5. Kaplan-Meier Graph of Primary Safety Endpoint Success Rate (ITT Population)

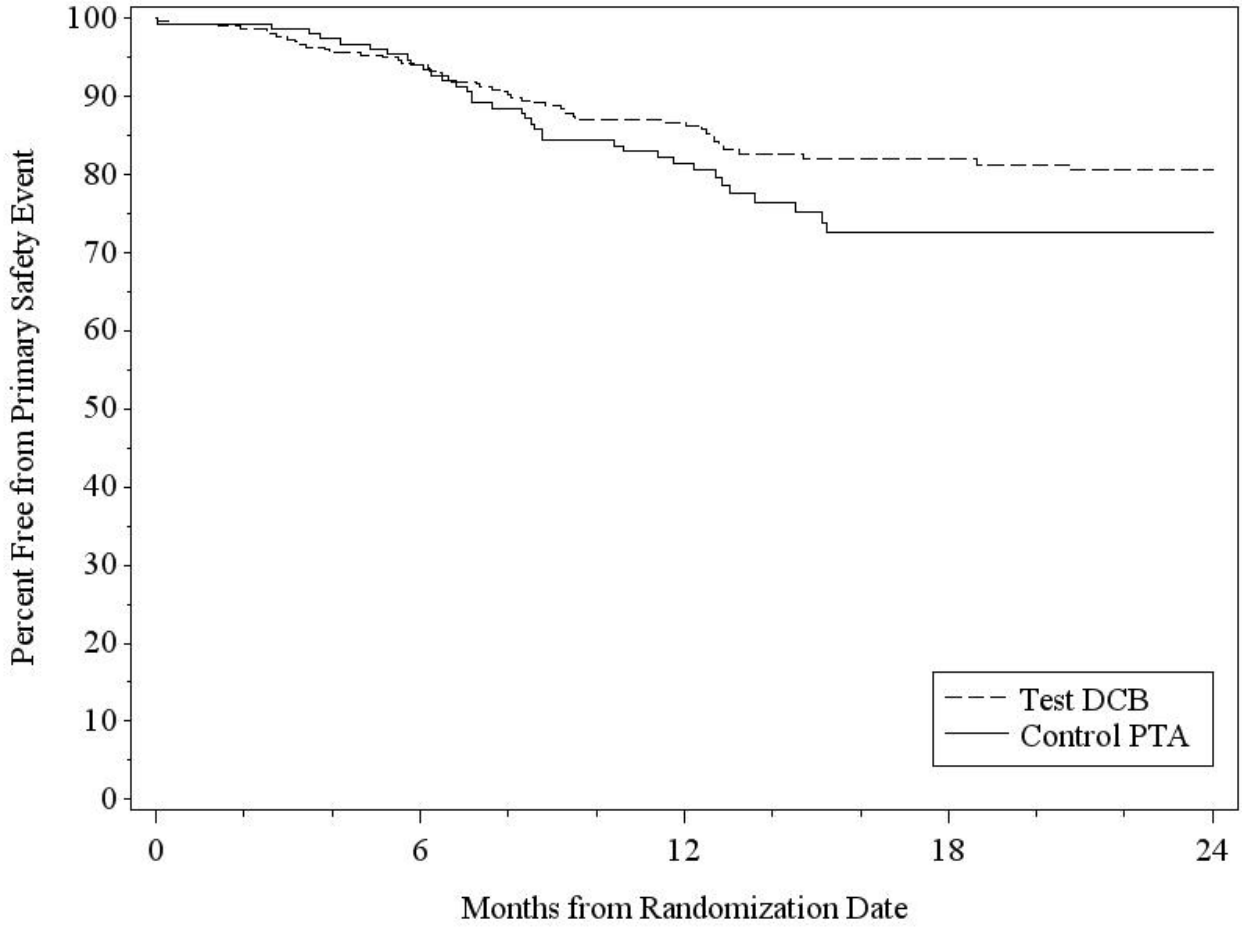


Table 12. Freedom from Primary Safety Endpoint by Kaplan-Meier (ITT Population)

Time	Test DCB				Control PTA			
	Survival[1] %	Subjects with Event	Censored Subjects	Subjects at Risk	Survival %	Subjects with Event	Censored Subjects	Subjects at Risk
30 days	99.4%	2	9	305	99.4%	1	5	154
183 days	94.0%	18	21	277	94.1%	9	13	138
365 days	86.7%	39	66	211	81.5%	27	35	98
730 days	80.6%	50	226	40	72.6%	35	108	17

[1] Survival is the absence of the composite endpoint of failure from all-cause perioperative (≤30 day) death, index limb amputation (above or below the ankle), index limb re-intervention, or index-limb-related death.

SAE Listing

Serious adverse events are summarized in **Table 13**. Roughly half of the subjects in each treatment group experienced at least one SAE during the study. While differences in incidence in Lutonix DCB and control PTA subjects can be observed for some events, the disparity in incidence was not statistically or clinically significant. Overall, there was no evidence that treatment with the Lutonix DCB led to increased risk of any SAE.

Table 13. CEC-adjudicated Serious Adverse Events Through the 24-Month Follow-up Window (AT Population)

AE Category	Event code	DCB Subjects		PTA Subjects	
		n events	N=316 % (n subjects)	n events	N=160 % (n subjects)
1 Cardiac Events	1.01 Angina	15	4.4% (14)	3	1.9% (3)
	1.02 Atrial Fibrillation	3	0.9% (3)	2	1.3% (2)
	1.05 Other Arrhythmia, specify:	1	0.3% (1)	2	1.3% (2)
	1.06 Cardiac arrest/failure	1	0.3% (1)	0	0.0% (0)
	1.07 Hypertension (req. therapy)	1	0.3% (1)	1	0.6% (1)
	1.08 Hypotension (Sustained, req. pressors and/or IABP)	2	0.6% (2)	0	0.0% (0)
	1.09 MI: Q-wave (STEMI)	0	0.0% (0)	1	0.6% (1)
	1.10 MI: Non Q-wave (NSTEMI)	4	0.9% (3)	1	0.6% (1)
	1.11 MI: Unknown	4	1.3% (4)	2	1.3% (2)
	1.13 CHF: After discharge	9	1.9% (6)	0	0.0% (0)
	1.14 Other Cardiac, specify:	5	1.3% (4)	1	0.6% (1)

AE Category	Event code	DCB Subjects		PTA Subjects	
		n events	N=316 % (n subjects)	n events	N=160 % (n subjects)
2 Clinical Events	2.01 Contrast media allergic reaction	1	0.3% (1)	0	0.0% (0)
	2.05 Fever, unknown etiology	1	0.3% (1)	0	0.0% (0)
	2.06 Groin infection, local (req. antibiotics)	1	0.3% (1)	0	0.0% (0)
	2.07 Skin infection, local (req. antibiotics)	2	0.6% (2)	1	0.6% (1)
	2.08 Other infection, local (req. antibiotics), specify:	6	1.9% (6)	1	0.6% (1)
	2.09 Infection, systemic (req. antibiotics)	2	0.6% (2)	1	0.6% (1)
	2.10 Renal insufficiency (> 0.5 increase in Cr from preprocedure/baseline)	3	0.9% (3)	1	0.6% (1)
	2.11 Renal failure (requiring new dialysis or prolonged hospitalization with dialysis)	0	0.0% (0)	0	0.0% (0)
	2.12 Respiratory failure: Fluid volume overload	0	0.0% (0)	0	0.0% (0)
	2.13 Respiratory failure: Exacerbation of COPD	8	1.6% (5)	1	0.6% (1)
	2.16 Pneumonia	8	2.5% (8)	2	1.3% (2)
	2.17 Neoplasia	15	3.8% (12)	9	5.0% (8)
	2.18 Pulmonary Embolism	2	0.6% (2)	0	0.0% (0)
	2.19 Other Clinical, specify:	13	3.2% (10)	6	2.5% (4)
	2.20 Orthopaedic Injury	5	1.6% (5)	4	2.5% (4)
	2.21 Orthopaedic Disease	7	1.9% (6)	5	2.5% (4)
	2.22 Musculoskeletal Pain	2	0.6% (2)	0	0.0% (0)
	2.23 Arthritis/gout	0	0.0% (0)	1	0.6% (1)
	2.24 Other Renal Events	6	0.9% (3)	0	0.0% (0)
	2.25 Gastrointestinal Disorder	6	1.9% (6)	8	4.4% (7)
	2.26 Inguinal hernia	2	0.6% (2)	0	0.0% (0)
	2.27 Cholelithiasis	0	0.0% (0)	1	0.6% (1)
	2.28 Benign Prostatic Hypertrophy	1	0.3% (1)	0	0.0% (0)
	2.29 Cataracts	5	1.3% (4)	3	1.3% (2)
	2.32 Electrolyte Abnormality	3	0.9% (3)	0	0.0% (0)
	2.33 Dyspnea	1	0.3% (1)	0	0.0% (0)
	2.34 Non-Cardiac Chest Pain	4	1.3% (4)	0	0.0% (0)
	2.38 Cholecystitis	1	0.3% (1)	1	0.6% (1)

AE Category	Event code	DCB Subjects		PTA Subjects	
		n events	N=316 % (n subjects)	n events	N=160 % (n subjects)
3 Hemorrhagic Events	3.01 Access site: Hematoma	3	0.9% (3)	0	0.0% (0)
	3.02 Access site: Significant hemorrhage req. transfusion	4	0.9% (3)	0	0.0% (0)
	3.03 Access site: Pseudoaneurysm	4	1.3% (4)	3	1.9% (3)
	3.06 Bleeding/Hemorrhage from anticoagulants	2	0.6% (2)	0	0.0% (0)
	3.07 Bleed, Gastrointestinal	4	1.3% (4)	1	0.6% (1)
	3.09 Bleed, Retroperitoneal	2	0.6% (2)	1	0.6% (1)
	3.10 Anemia, general (req. blood transfusion)	4	0.9% (3)	1	0.6% (1)
	3.11 Other Hemorrhage, specify:	5	1.3% (4)	1	0.6% (1)
4 Neurological Events	4.01 TIA (Focal deficit resolving within 24 hours)	2	0.6% (2)	0	0.0% (0)
	4.02 Stroke (Focal deficit lasting over 24 hours)	9	2.8% (9)	1	0.6% (1)
	4.03 Other Neurologic, specify:	4	1.3% (4)	4	2.5% (4)
	4.05 Hearing loss	1	0.3% (1)	0	0.0% (0)
	4.06 syncope/near syncope/dizziness/vertigo	4	1.3% (4)	0	0.0% (0)
5 Angiographic Events	5.02 Target vessel injury/dissection with pre-treatment	0	0.0% (0)	0	0.0% (0)
	5.03 Target vessel injury/dissection with study treatment	6	1.9% (6)	6	3.8% (6)
	5.04 Target vessel injury/dissection with post-treatment	1	0.3% (1)	2	1.3% (2)
	5.07 Distal embolization with study treatment	1	0.3% (1)	1	0.6% (1)
	5.08 Distal embolization with post-treatment	0	0.0% (0)	1	0.6% (1)
	5.10 Arterial rupture	1	0.3% (1)	0	0.0% (0)
	5.11 Clot/Thrombus formation (thrombosis)	1	0.3% (1)	2	1.3% (2)
	5.15 Access Site Dissection	1	0.3% (1)	0	0.0% (0)
	5.17 Distal embolization (non-index procedure)	1	0.3% (1)	0	0.0% (0)

AE Category	Event code	DCB Subjects		PTA Subjects	
		n events	N=316 % (n subjects)	n events	N=160 % (n subjects)
6 Vascular Events	6.02 Restenosis of the study lesion	5	1.6% (5)	7	3.8% (6)
	6.03 Restenosis of the study vessel	1	0.3% (1)	2	1.3% (2)
	6.04 Restenosis of the non-study vessel	24	7.0% (22)	10	6.3% (10)
	6.05 Clinically-driven target (study) lesion revascularization (TLR)	6	1.9% (6)	2	1.3% (2)
	6.06 Incidental target (study) lesion revascularization (TLR)	0	0.0% (0)	1	0.6% (1)
	6.07 Target (study) vessel revascularization (TVR)	0	0.0% (0)	0	0.0% (0)
	6.09 Target (study) extremity revascularization (non-study lesion/vessel)	0	0.0% (0)	1	0.6% (1)
	6.10 Non-target extremity revascularization	5	1.3% (4)	6	3.8% (6)
	6.11 Non-target acute limb ischemia	2	0.6% (2)	0	0.0% (0)
	6.12 Target (study) acute limb ischemia	1	0.3% (1)	0	0.0% (0)
	6.17 Non-target extremity minor/major amputation, toe(s)	0	0.0% (0)	0	0.0% (0)
	6.22 Target extremity pain	12	3.2% (10)	5	3.1% (5)
	6.24 Target extremity ischemic ulcer-New	2	0.6% (2)	0	0.0% (0)
	6.25 Non-target extremity pain	9	2.8% (9)	4	2.5% (4)
	6.27 Non-target extremity ischemic ulcer-New	0	0.0% (0)	1	0.6% (1)
	6.28 Other Vascular, specify:	2	0.6% (2)	2	1.3% (2)
	6.29 Bilateral lower extremity pain	1	0.3% (1)	3	1.9% (3)
	6.31 Deep vein thrombosis	0	0.0% (0)	0	0.0% (0)
	6.32 Non target limb aneurysm	1	0.3% (1)	0	0.0% (0)
	6.35 Claudication	50	12.3% (39)	40	16.9% (27)
7 Other Events	7.01 Other, specify:	1	0.3% (1)	0	0.0% (0)
8 Non-Event/ Death Outcomes	8.01 Accidental death	0	0.0% (0)	1	0.6% (1)
	8.03 Cardiac death	1	0.3% (1)	0	0.0% (0)
	8.04 Sudden cardiac death	0	0.0% (0)	1	0.6% (1)
	8.06 Unknown cause of death	4	1.3% (4)	1	0.6% (1)
	8.07 Death (not otherwise specified-NOS)	0	0.0% (0)	0	0.0% (0)
	8.08 Death from neoplasia	1	0.3% (1)	0	0.0% (0)
Total	Total	338	53.5% (169)	169	50.0% (80)

9.1.6.2 Primary Efficacy Endpoint Evaluation

The Primary Efficacy Endpoint is primary patency defined as the absence of binary restenosis and absence of clinically-driven target lesion revascularizaton (TLR) at 12 months.

Overall, 83.5% (264/316) Lutonix DCB subjects and 84.4% (135/160) control PTA subjects were evaluable for the primary efficacy endpoint testing. Missing subjects included 7.9% (25) Lutonix DCB and 6.9% (11) control PTA subjects who either died, withdrew, or were lost-to-follow-up without prior efficacy failures, 6.0% (19) Lutonix DCB and 5.6% (9) control PTA subjects with 12-month clinical follow-up but non-analyzable or missing DUS, and 2.5% (8) Lutonix DCB and 3.1% (5) control PTA subjects with missed visits at 12 months and no prior failure.

The proportion of subjects with primary patency at 12 months was 65.2% in the Lutonix DCB group and 52.6% in the standard PTA group, and superior efficacy (p = 0.015) of Lutonix DCB over control PTA was demonstrated – see **Table 14**.

Table 14. Primary Patency of Target Lesion (ITT Population)

Measure	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference % [95% CI]	P-value[2]
Primary Patency[1]	65.2% (172/264) [59.4, 70.9]	52.6% (71/135) [44.2, 61.0]	12.6% [2.4, 22.8]	0.015

[1]Primary Patency is defined freedom from target lesion restenosis (defined by DUS core lab adjudication) and target lesion revascularization (TLR).
[2]Based on asymptotic likelihood ratio test. CIs for groups and difference are asymptotic.

Kaplan-Meier survival analysis

Primary patency has also been analyzed using time-to-event Kaplan-Meier survival analysis as part of the sensitivity analyses to address missing data. Primary patency by Kaplan-Meier analysis (**Table 15** and **Figure 6**) was consistent with the superiority of primary patency of Lutonix DCB over control PTA that was demonstrated by proportion-based hypothesis testing. At 365 days, the primary patency rate was 73.5% for the Lutonix DCB group compared to 56.8% for the control PTA group.

Figure 6. Kaplan-Meier Graph of Primary Patency (ITT Population)

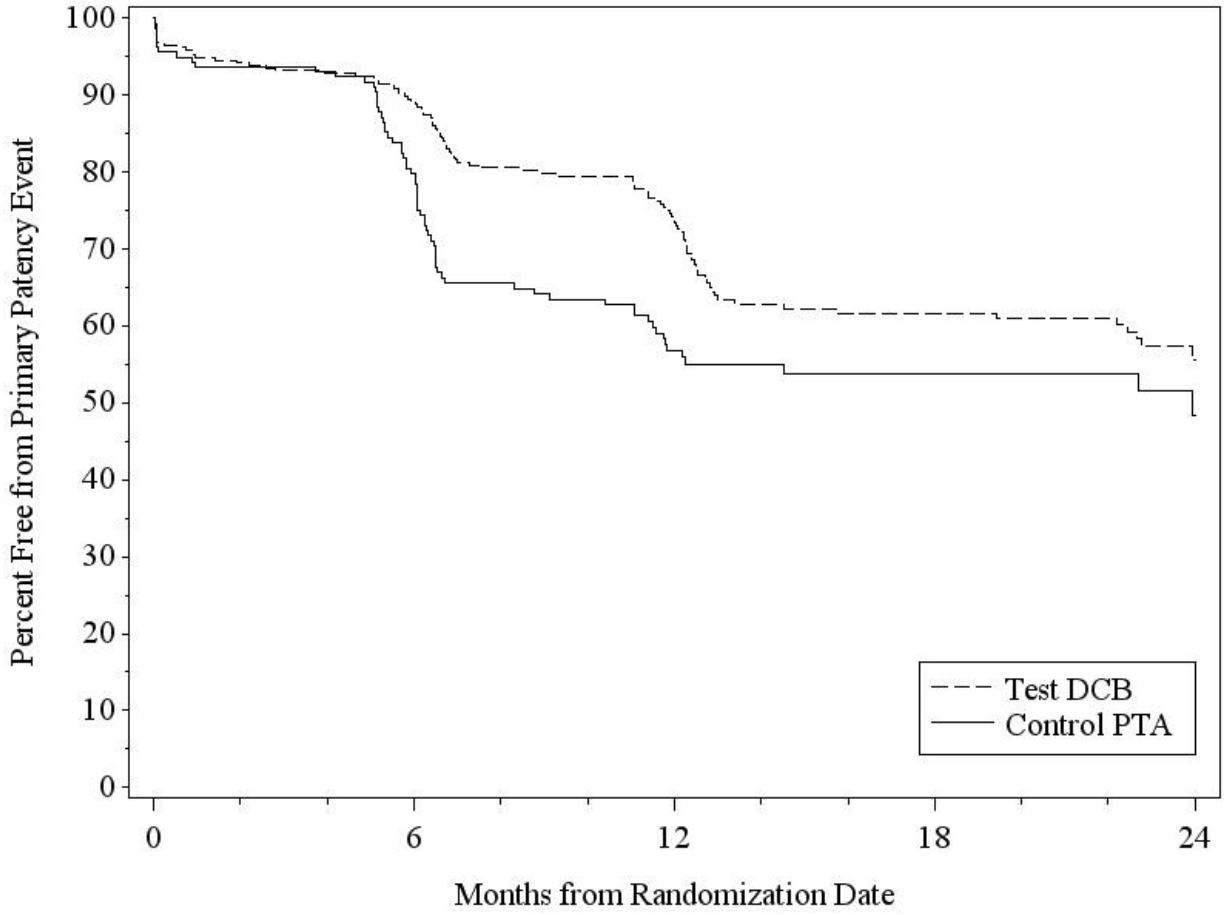


Table 15. Primary Patency by Kaplan-Meier Analysis (ITT Population)

	Test DCB				Control PTA			
Time[1]	Survival[1] %	Subjects with Event	Censored Subjects	Subjects at Risk	Survival %	Subjects with Event	Censored Subjects	Subjects at Risk
30 days	94.9%	16	9	291	93.7%	10	4	146
183 days	88.8%	34	21	261	78.5%	33	11	116
365 days	73.5%	77	60	179	56.8%	64	27	69
730 days	53.7%	108	182	26	48.4%	69	77	14

[1] Primary Patency success is defined as the absence of target lesion restenosis (defined by core lab adjudication) and freedom from target lesion revascularization (TLR).

9.1.6.3 TLR at 12 months

TLR rates at 12 month follow-up were similar for Lutonix DCB and control PTA groups, although trending favorable for Lutonix DCB.

Table 16. TLR rate at 12 Months

Measure	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference % [95% CI]	P-value[1]
Total TLR at 12 Months	12.3% (35/285) [8.5, 16.1]	16.8% (24/143) [10.7, 22.9]	-4.5% [-11.7, 2.7]	0.208

[1] Based on asymptotic Likelihood Ratio test. CIs for groups and difference are asymptotic.

9.1.7 Pharmacokinetic Sub-Study

Pharmacokinetic testing for blood paclitaxel level was performed on a sub-set of 22 Lutonix DCB subjects from 7 different sites. Blood samples were collected several times prior to patient discharge and at 30-day follow-up.

Evidence of systemic paclitaxel amount was observed in all tested subjects before discharge, but no drug was detected in any of the 30-day follow-up samples. The pharmacokinetics of paclitaxel generally exhibited a bi-exponential decay; characterized by a rapid distribution phase followed by a log-linear elimination phase. Following Lutonix DCB treatment, group mean (SD) values for C_{max}, AUC_{all}, and MRT_{last} were 5.10 (3.21) ng/mL, 8.39 (4.00) ng*h/mL, and 2.13 (1.84) h, respectively. The mean elimination half-life was estimated at 6.88 h for evaluable subjects; however, blood sampling was very limited in the study.

9.1.8 LEVANT 2 Study Conclusion

The Lutonix DCB is an angioplasty balloon coated with the drug paclitaxel. The Lutonix DCB is indicated for percutaneous transluminal angioplasty of obstructive de novo or non-stented restenotic lesions in native femoropopliteal arteries ≤ 150 mm in length and 4-6 mm in reference vessel diameter. Like all angioplasty balloons, the immediate result of treatment is the opening of the blocked artery by balloon dilatation, and procedural success of Lutonix DCB was comparable to that of control balloon angioplasty (88.9% vs. 86.8%). The ancillary benefit of the paclitaxel drug coating is to improve the durability of patency by reducing restenosis over time without leaving metal behind. The LEVANT 2 Randomized trial is a prospective, multicenter, single blind, randomized, controlled trial of 476 randomized subjects that successfully met both co-primary (safety and efficacy) endpoints at 12 months by direct comparison to conventional balloon angioplasty (control PTA).

At 12 months, primary patency of the Lutonix DCB group was superior to that of the standard PTA group (65.2% vs. 52.6%, p = 0.015). Primary safety (freedom from 30-day all cause perioperative death and 12-month index limb-related death, amputation, and revascularization) of DCB was non-inferior to control PTA (83.9% vs. 79.0%, p = 0.005). Use of paclitaxel-coated balloons provided better efficacy with a similar safety profile to control PTA balloons.

No safety risks were observed that might counterbalance the demonstrated efficacy benefit. Treatment of native femoropopliteal lesions with Lutonix DCB provides more durable patency than PTA without increasing safety risk.

9.2 LEVANT 1 Randomized European Study

9.2.1 Study Design

The Lutonix LEVANT I trial was a prospective, multicenter, single blind, randomized trial comparing the Lutonix Catheter (Model 9003, 0.018" guidewire compatible version) vs. standard PTA catheter (POBA – plain old balloon angioplasty) for treatment of femoropopliteal arteries with and without stenting. The LEVANT I trial enrolled subjects presenting with clinical evidence of claudication or critical limb ischemia (CLI) and an angiographically significant lesion in the femoropopliteal arteries. After pre-dilatation of the lesion, subjects were stratified based on pre-defined criteria to undergo PTA only (Balloon Group, with provisional bail-out stenting only if necessary) or stenting with post-dilatation (Stent Group). Subjects in each stratification group were then randomized to treatment with either the Lutonix Catheter (test arm) or standard uncoated balloon angioplasty (POBA control arm). See **Figure 7** for a schematic of the treatment flow and **Table 17** for the study design overview.

Figure 7: Flowchart of Subject Randomization

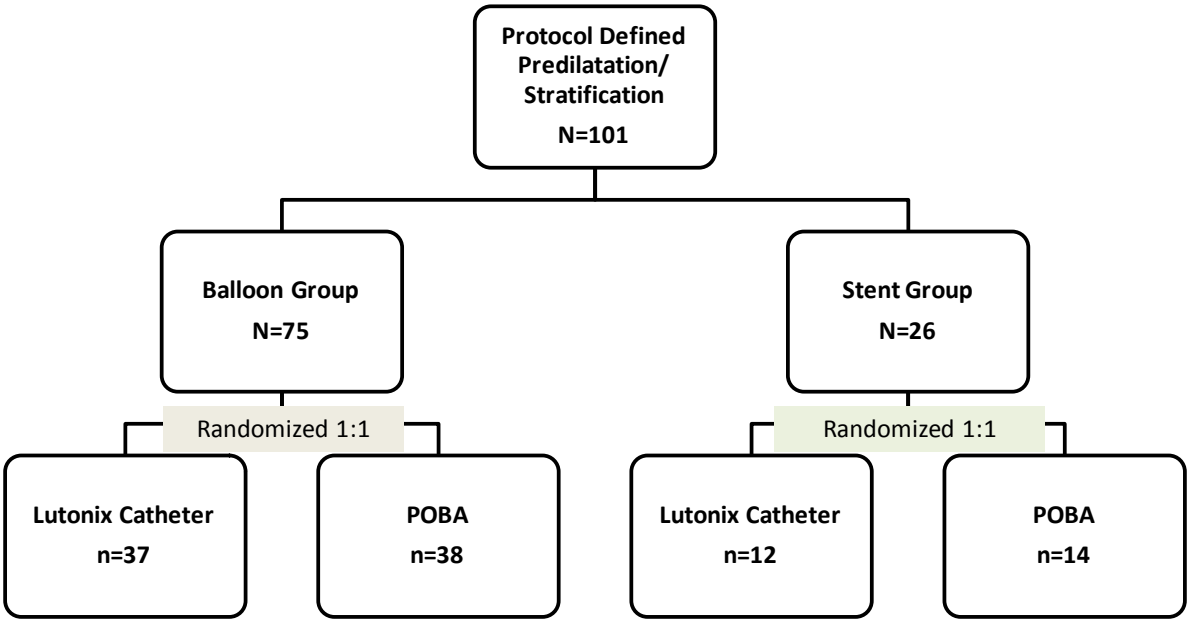


Table 17. LEVANT 1 Randomized Trial Study Design

Item	Description
Study Type/Design	Prospective, Multicenter, Single Blind, Randomized, Safety and Efficacy
Study Objective	The objective of the LEVANT I Clinical Study was to assess the safety and efficacy of the Lutonix Catheter for treatment of stenosis of the femoropopliteal arteries by direct comparison to standard balloon angioplasty (POBA). The primary endpoint was angiographic late lumen loss (LLL) at 6 months, as determined by an independent angiographic core lab analysis.
Number of Subjects Enrolled	101 patients (75 balloon group and 26 stent group), see **Figure 7** above.

Treatment Lesion	De novo or restenotic angiographically significant lesion in the superficial femoral or popliteal artery with lesion length of ≤ 15 cm in length and reference vessel of 4 mm – 6 mm in diameter.
Treatment Device	Test Arm: LUTONIX® Catheter (Model 9003, 0.018" guidewire compatible) Control Arm: Non-coated standard percutaneous transluminal angioplasty balloon catheter (standard PTA catheter)
Balloon Sizes	Balloon Diameters: 5 mm & 6 mm Balloon Lengths: 60 mm and 100 mm in length.
Post-procedure Antiplatelet Therapy	Appropriate antiplatelet therapy (clopidogrel) for at least 30-days (Balloon group) and 3 months (Stent group) and aspirin indefinitely.
Primary Endpoints	Angiographically assessed late lumen loss (LLL) at 6 months.
Randomized Subject Follow-Up Schedule	*Clinical*: 6, 12, and 24 Months *Duplex Ultrasound (DUS):* 6, 12, and 24 months
Status	24 month Final Report completed.

9.2.2 Dataset

The primary analysis dataset includes data for all subjects on an intent-to-treat (ITT) basis, and data for all subjects randomized to Lutonix Catheter are compared to data for all subjects randomized to POBA.

All data reported in the body of this report reflect data reported by the CRO and were 100% monitored to the source data. Subset analyses and primary patency based on alternative censoring methods and alternative threshold PSVRs indicating restenosis were independently calculated by the Integra Group (statistical consultant) from data provided by the CRO.

9.2.3 Demographics and Baseline Lesion Characteristics

The mean age of enrolled subjects was 68±9 years, 63% were male, 35% were current smokers, 34% were previous smokers and 48% had Type II diabetes mellitus. At baseline examination, 71% of the subjects were rated a Rutherford Category 3, 22% were Rutherford Category 2, and the remaining 7% were Rutherford Category 4 and 5. More than 40% reported previous coronary artery disease, and other co-morbidities (renal disease, congestive heart failure, cerebrovascular disease and structural heart disease) were common. There were no statistically significant differences between the groups for any demographic or medical history factor.

By quantitative vascular angiography (QVA), mean lesion length was 8.1±3.7 and 8.0±3.8cm and RVD was 4.1±0.6 and 4.2±0.7mm in the Lutonix Catheter and control POBA arms, respectively. Eighty nine percent of treated lesions were de novo lesions, with the majority located in the mid and distal portions of the SFA. Popliteal lesions were treated in 4 (8.2%) test and 3 (5.8%) control cases.

The overall rate of concomitant stent implantation and procedural characteristics were similar in both randomized groups. In the Lutonix Catheter arm, there were 8 (16%) device malfunctions due to a twisted balloon fold manufacturing defect that resulted in failure to completely inflate in target lesions.

9.2.4 Safety and Effectiveness Results

9.2.4.1 Primary Endpoint Results - Angiographic Late Lumen Loss at 6 Months

Angiographic data was evaluable for 74 subjects, including 39/49 (80%) of Lutonix Catheter and 35/52 (67%) of POBA subjects.

The Primary Endpoint of mean late lumen loss in the analysis segment at 6 months was 0.46 ± 1.13 mm in the Lutonix Catheter arm compared to 1.09 ± 1.07mm in the POBA arm (p = 0.016) in the ITT population.

In the balloon-only strata, mean late lumen loss was 0.45 ± 1.18mm in the Lutonix Catheter arm vs. 1.19 ± 1.15 mm in the POBA arm (p = 0.024). The difference between arms was not significant in the stent group, with late loss of 0.49 ± 1.01 for Lutonix vs. 0.90 ± 0.91 for POBA, p = 0.373.

Based on freedom from angiographic binary restenosis, primary patency of the treated segment was 28 of 39 (71.8%) for Lutonix Catheter and 17 of 35 (48.6%) for POBA at 6 months.

9.2.4.2 Safety and Efficacy Endpoints

Eighty-six (86) subjects had 12 month clinical follow-up, including 92% (45/49) Lutonix Catheter and 79% (41/52) POBA subjects. Six (6) subjects died (2 Lutonix Catheter, 4 POBA), 7 withdrew consent (2 Lutonix Catheter, 5 POBA), and 2 were lost to follow-up (both POBA).

Twenty-four month information is available for 92% (45/49) Lutonix Catheter and 82% (42/51) POBA subjects, including subjects that died. Seventy-nine (79) subjects had 24 month follow-up, including 84% (41/49) Lutonix Catheter and 73% (38/52) POBA subjects. Since study commencement, 9 subjects died (4 Lutonix Catheter, 5 POBA), 7 withdrew consent (2 Lutonix Catheter, 5 POBA), and 6 were lost to follow-up (2 Lutonix Catheter, 4 POBA).

At completion of the study, the percentage of enrolled subjects with any death, amputation, or target vessel thrombosis was 8% (4/49) for Lutonix Catheter compared to 12% (6/52) for control POBA – reference **Table 18** below. Deaths in the Lutonix Catheter arm were due to cancer (1), sepsis (1), and cardiac (2). Deaths in the control arm were due to cancer (1) and cardiac (4). There were no target vessel thromboses and 1 amputation (subject later died) in the Lutonix Catheter arm and one target vessel thrombosis (subject later withdrew) in the control arm. Composite major adverse events were 39% (19 of 49) for Lutonix DCB, including 15 TLRs, 1 amputation, and 4 deaths vs. 46% (24 of 52) for uncoated POBA control, with 20 TLRs, 1 thrombosis, and 5 deaths. Note: a given subject may have more than one event.

Through study completion at 24 months follow-up, a total of 35 subjects in the ITT population had a CEC-adjudicated TLR, including 36% (15/42) in the Lutonix Catheter arm and 49% (20/41) in the control POBA arm – reference **Table 19** . Only one subject had a TVR without having a TLR, for a TVR rate of 36% (15/42) in the Lutonix Catheter arm compared to 51% (21/41) in the control POBA arm.

Primary patency (PSVR < 2.5) was 57.1% (24/42) for Lutonix Catheter compared to 39.5% (17/43) for control POBA – reference **Table 20** below.

Table 18: Cumulative Adverse Events as Adjudicated by CEC

Adverse event type through Designated Follow Up *(number of subjects having any events and total number of events)*	Through 12 Months		Through 24 Months	
	Lutonix Catheter N=49 n (total events)	**POBA N=52 n (total events)**	**Lutonix Catheter N=49 n (total events)**	**POBA N=52 n (total events)**
Non-serious AE[1]	23 (32)	29 (51)	28 (50)	31 (74)
SAE[1]	33 (66)	34 (80)	39 (90)	39 (110)
Thrombosis (target vessel)	0 (0)	1 (1)	0 (0)	1 (1)
Amputation	1 (1)	0 (0)	1 (1)	0 (0)
Death	3 (3)	4 (4)	4 (4)	5 (5)
TLR	13 (17)	14 (14)	15 (20)	20 (21)
TVR	13 (17)	15 (19)	15 (20)	21 (26)

[1] Any given subject may have more than one reported AE or SAE. SAEs reported at 24 Months follow-up that occurred within the 12 Month follow-up time window (395 days) are included at 12 Months.

Table 19: Target Lesion Revascularization, 12 and 24 months (ITT)

Subgroup	12 Months		24Months	
	Lutonix % (n/N)	**POBA % (n/N)**	**Lutonix % (n/N)**	**POBA % (n/N)**
All Patients	28.9% (13/45)	33.3% (14/42)	35.7% (15/42)	48.8% (20/41)
Balloon-only Strata	35.3% (12/34)	34.5% (10/29)	43.8% (14/32)	50.0% (14/28)
Stent Strata	9.1% (1/11)	30.8% (4/13)	10.0% (1/10)	46.2% (6/13)

Table 20: Primary Patency at 12 and 24 months (Failure must be proven by DUS) - ITT

Threshold for Restenosis Subgroup	12 Months		24 Months	
	Lutonix % (n/N)	**POBA % (n/N)**	**Lutonix % (n/N)**	**POBA % (n/N)**
DUS PSVR ≥ 2.5	**66.7% (30/45)**	**54.8% (23/42)**	**57.1% (24/42)**	**39.5% (17/43)**
Balloon-only Strata	61.8% (21/34)	51.7% (15/29)	50.0% (16/32)	40.0% (12/30)
Stent Strata	81.8% (9/11)	61.5% (8/13)	80.0% (8/10)	38.5% (5/13)

9.2.5 LEVANT 1 Study Conclusions

In LEVANT 1 randomized, controlled clinical study, the Lutonix Catheter met the primary objective and demonstrated significantly less late lumen loss at 6 months and similar safety through 24 months by direct comparison to conventional balloon angioplasty.

In the ITT population, the primary endpoint of mean Late Lumen Loss at 6 months was better in the Lutonix Catheter arm (0.46±1.13) compared to the POBA arm (1.09±1.07), with a p-value of 0.016. The difference in mean late loss between arms was also lower in the balloon-only stratification group (0.45±1.18 vs. 1.19±1.15, p=0.024).

The Lutonix Catheter demonstrated safety comparable to conventional angioplasty (POBA) in the LEVANT I Trial, with similar ITT AE and SAE rates through 24 months. There were no unanticipated adverse device effects in the drug-coated balloon arm, and overall adverse event rates were similar to conventional uncoated balloon angioplasty.

10 HOW SUPPLIED

- **Sterile:** This device is sterilized with ethylene oxide gas. Do not use if package is opened or damaged. For one use only. Do not resterilize.
- The LUTONIX® Catheter has a protective sheath placed over the balloon, is stored within a standard dispensing hoop, and is sterilized within a dual chamber pouch. The dual chamber pouch contains both a catheter compartment and desiccant compartment. The compartments are separated by a sterile barrier. The desiccant compartment contains packets used to help control package environment and should not be opened.
- **Contents**: One (1) LUTONIX® 035 Drug Coated Balloon PTA Catheter.
- **Storage:** Store in a dry, dark place. Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Do not store near radiation or ultra-violet light sources.

11 DIRECTIONS FOR USE

11.1 Equipment

In addition to the LUTONIX® Catheter, the following standard materials may also be required:

- 0.035″ Guidewire
- Introducer sheath
- Contrast medium
- Sterile saline
- Inflation device with manometer
- Luer lock syringe for purging

11.2 Inspection Prior to Use

Prior to angioplasty, carefully examine all equipment to be used during the procedure, including the dilatation catheter, to verify proper function. Verify that the catheter and sterile packaging have not been damaged in shipment.

Warning: Contents supplied STERILE using ethylene oxide (EO) process. Do not use if sterile barrier is damaged or opened prior to intended use.

11.3 Use of Multiple LUTONIX® Catheters

- If multiple LUTONIX® Catheters are required to complete treatment of a lesion, the sequentially used LUTONIX® Catheter should be minimally sized and angiographically positioned so that the marker bands of consecutively placed balloons overlap as necessary to cover the lesion and margins of the predilatation segment. The LUTONIX® Catheter should extend a minimum of 5 mm proximally and distally from the lesion and injury segment. Care should be taken not to extend the entire injury segment(s) unnecessarily. The use of a radiopaque ruler is recommended to ensure appropriate placement of the LUTONIX® Catheter. See **Figure 8**.

  Precaution: Use of more than two LUTONIX® Catheters deployed in a single target lesion during a single procedure has not been assessed.

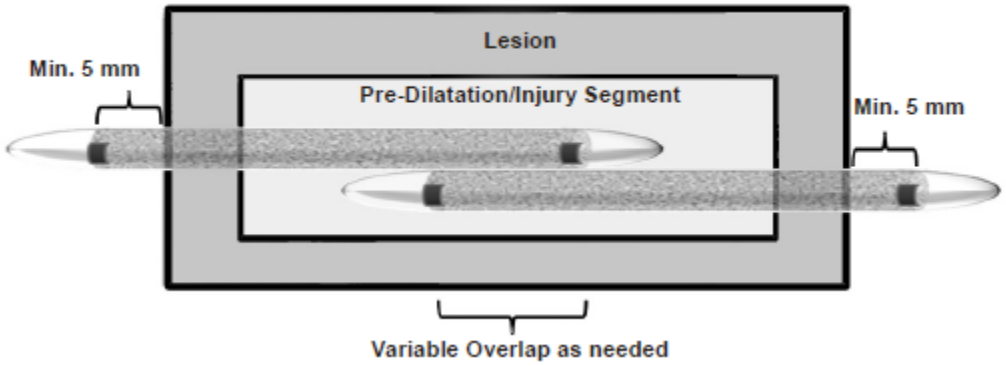


Figure 8: Balloons are appropriately sized to minimize overlap but are consecutively placed by angiography with as much overlap as necessary to treat lesion appropriately

11.4 Lutonix® Catheter Preparation

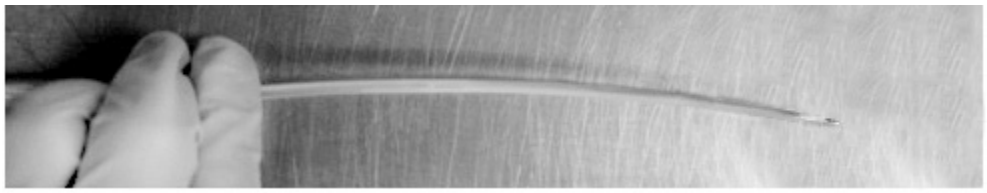
1. Remove the device from the packaging.
2. Verify the balloon size is suitable for the procedure and the selected accessories are compatible with the catheter as labeled.
3. Prepare the inflation device/syringe with diluted contrast medium.

   Warning: Use the recommended balloon inflation medium of contrast and sterile saline (≤50% contrast). Never use air or any gaseous medium to inflate the balloon.
4. Prior to use, the air in the balloon catheter should be removed. To facilitate purging, select a syringe or inflation device with a 10 ml or larger capacity and fill approximately half of it with the recommended contrast medium.
5. Connect a stopcock to the balloon inflation female luer hub on the dilatation catheter.
6. Connect the syringe to the stopcock.
7. Hold the syringe with the nozzle pointing downward, open the stopcock and aspirate for approximately 15 seconds. Release the plunger.
8. Repeat from **step 4** above as needed until bubbles no longer appear during aspiration (negative pressure). Once completed, evacuate all air from the barrel of the syringe/inflation device.

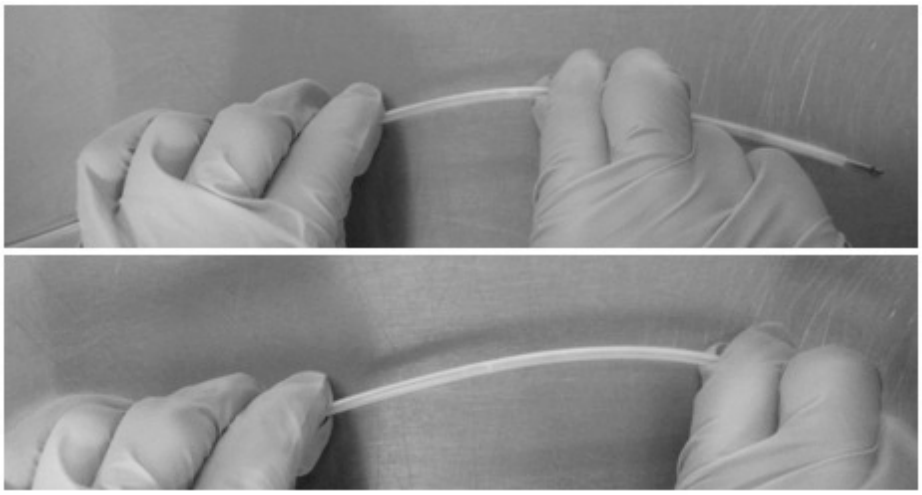
11.5 Use of the Lutonix® Catheter

1. While under negative pressure and before removing the balloon protector and wire lumen stylet, perform the following steps to reduce friction between the balloon protector and the balloon and remove the balloon protector:

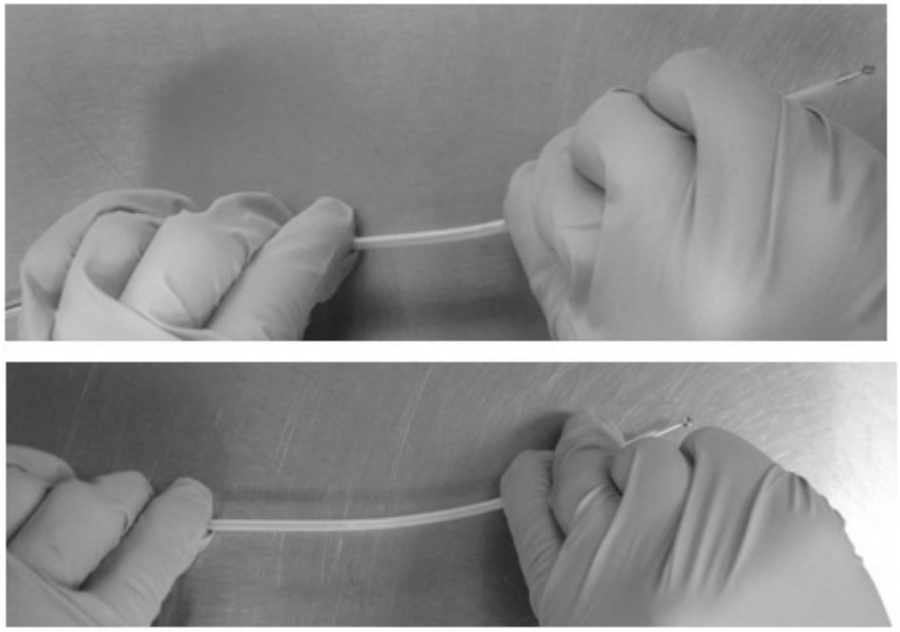
   Step 1- Leaving the wire lumen stylet in place; grasp the proximal end of the balloon protector with one hand.



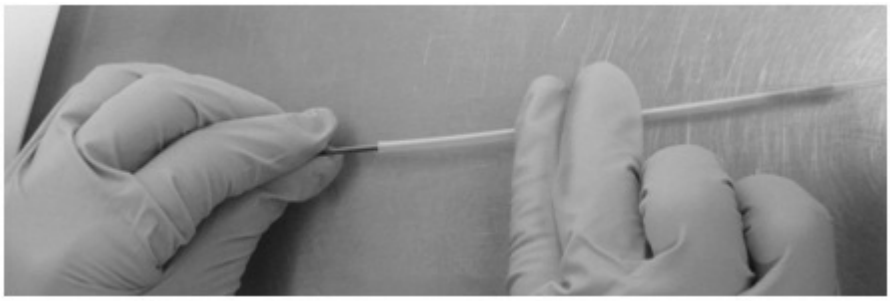
Step 2- Using the opposite hand, gently slide the thumb and forefinger from the proximal end of the balloon protector out toward the distal end of the balloon protector while flexing the balloon slightly downward approximately 15 degrees.

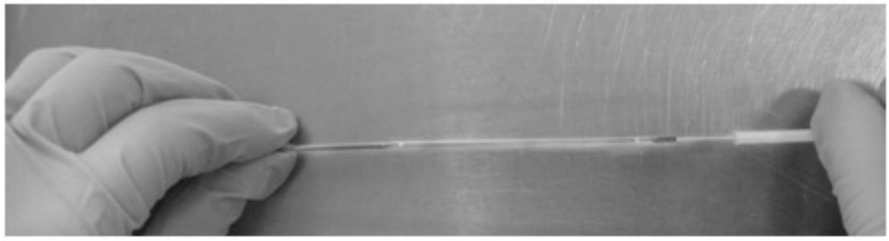


Step 3- Repeat Step 2, but flex the balloon protector upward approximately 15 degrees.



Step 4- Grasp the balloon protector at roughly the midpoint of the balloon protector and pull it away from the balloon catheter. The balloon protector and wire lumen stylet should be removed together.





2. With the catheter tip oriented down/vertically, flush the wire lumen.
3. Backload the distal tip of the dilatation catheter onto the guidewire.
4. While the balloon is still fully deflated and under negative pressure, slowly advance the Lutonix® Catheter through the introducer sheath and over the wire to the site of inflation. During catheter advancement, inspect the catheter shaft for damage.
5. To ensure therapeutic drug delivery, the Lutonix® Catheter should be advanced to the target site in an efficient manner (≤ 3 minutes) and immediately inflated.

   Warning: Do not exceed the Rated Burst Pressure (RBP) recommended for this device. Balloon rupture may occur if the RBP rating is exceeded. To prevent over-pressurization, use of a pressure monitoring device is recommended.
6. Position the balloon relative to the lesion, ensuring coverage of at least 5mm proximally and distally beyond the margins of the lesion segment, and inflate the balloon to the appropriate pressure (reference Compliance Chart included on product label). The use of a radiopaque ruler is recommended to ensure appropriate placement of the Lutonix® Catheter.
7. Apply negative pressure to fully deflate the LUTONIX® Catheter. Prior to removal, confirm that the balloon is fully deflated under fluoroscopy.
8. Perform angiography to confirm dilatation of the lesion.
9. Withdraw the LUTONIX® Catheter from the body under negative pressure. Maintain the guidewire across the stenosis.
10. Whenever possible, the LUTONIX® Catheter should be the final treatment of the vessel; however, post-dilatation is allowed with another PTA catheter or used LUTONIX® catheter.
11. After confirming that a satisfactory dilatation was achieved, remove all equipment from the body and close access site per standard clinical practice.
12. Refer to **Section 5.6** for Pre- and Post-Procedure Antiplatelet Regimen for the dual antiplatelet pharmacological therapy recommended with use of the LUTONIX® Catheter.
13. After use, this product may be a potential biohazard. Handle and dispose of in accordance with acceptable medical practices and applicable laws and regulations.

12 DISCLAIMER OF WARRANTY

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